2012
CONFÉRENCE CANADIENNE
CONSENSUELLE SUR LA DÉMENCE

2012
CANADIAN CONSENSUS
CONFERENCE ON DEMENTIA

Canadian Consensus Conference on Dementia
2012
Conférence Canadienne Consensuelle sur la Démence

cccdtd4

Faculty/Presenter Disclosure

- **Faculty**: C. Patterson

- **Relationship with commercial interests:**

  - Grants/Research Support: CIHR, Heart & Stroke Foundation

  - Speakers Bureau/Honoraria: Nil

  - Consulting Fees: Nil

  - Other: In-kind support from Hamilton Health Sciences

- Canadian Consensus Conference on Assessment of Dementia (CCCAD) 1989
- Canadian Consensus Conference on Dementia 1999
- 3rd Canadian Consensus Conference on Diagnosis and Treatment of Dementia (cccdtd3) 2006
- 2012 Canadian Consensus Conference on Dementia (cccdtd4)

Reason for 2012 CCCD

- New definitions and conceptualization of AD
- Availability of biomarkers (e.g. CSF)
- New neuroimaging techniques (e.g. amyloid and functional MRI neuroimaging)
- Ethical concerns about clinical use (misuse) of biomarkers
- Target audience: non dementologist specialists, FMDs

Steering Committee

- Christopher Patterson (Co-Chair)
- Serge Gauthier (Co-Chair)
- Howard Chertkow
- Michael Gordon (Ethics consultant)
- Pedro Rosa-Neto
- Ken Rockwood (CDKTN)
- Jean-Paul Soucy

2012
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2012
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CONFERENCE ON DEMENTIA

- Posting background papers to website
- Comments added on line
- Voting online
- Advanced dissemination strategy (Alzheimer's & Dementia journal)

Montréal, May 4-5

2012

- Adherence to AGREE template
- Use of GRADE evidence classification
- Advanced knowledge translation strategy (DKTN, publications, web based)

AGREE Collaboration (Appraisal of Guidelines, research and Evaluation)

1. Scope and purpose: specific statement & description target population
2. Stakeholder involvement
3. Rigour of development: search strategy, criteria for selecting evidence, linkage to recommendations, external review
4. Clarity and presentation
5. Applicability: organization, cost, monitoring
6. Editorial independence: isolation from funding sources, conflict of interest declaration

Qual Saf Health Care 2003 12:18-23

GRADE: *Strong* evidence "We recommend…"

Grade of recommendation	Benefits vs. risks & burdens	Methodological quality of supporting evidence
Strong recommendation, high quality evidence 1A	Desirable effects clearly outweigh undesirable effects (or vice versa)	Consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies
Strong recommendation, moderate quality evidence 1B	Desirable effects clearly outweigh undesirable effects (or vice versa)	Evidence from RCTs with important limitations or very strong evidence from observational studies
Strong recommendation, low or very low quality evidence 1C	Desirable effects clearly outweigh undesirable effects (or vice versa)	Evidence for at least one critical outcome from observational studies, case series, RCTs with serious flaws or indirect evidence

GRADE: *Weak* evidence "We suggest…"

Grade of recommendation	Benefits vs. risks & burdens	Methodological quality of supporting evidence
Weak recommendation, high quality evidence 2A	Desirable effects closely balanced with undesirable effects	Consistent evidence from RCTs without important limitations or exceptionally strong evidence from observational studies
Weak recommendation, moderate quality evidence 2B	Desirable effects closely balanced with undesirable effects	Evidence from RCTs with important limitations or very strong evidence from observational studies
Weak recommendation, low or very low quality evidence 2C	Desirable effects closely balanced with undesirable effects	Evidence for at least one critical outcome from observational studies, case series, RCTs with serious flaws or indirect evidence

Process for achieving consensus: Electronic voting already recorded

- Consensus = 80% of CCCD participants
- Partial consensus = 60-79%
- Recommendation may be amended
- Less than 60%: option to drop or rewrite recommendation, opposing view
- Recommendations may be subsequently abbreviated for clarity

Definitions

H. Chertkow, H. Feldman, C. Jacova, F. Massoud

Definitions

	For
We recommend the adoption of the criteria for dementia proposed by the 2011 NIA-AA working group.	All
We recommend the adoption of the recommendations concerning probable and possible Alzheimer's Disease dementia core clinical diagnostic criteria proposed by the 2011 NIA-AA working group	All
We recommend the adoption of the core clinical criteria for MCI proposed by the 2011 NIA-AA working group	All
We recommend the 2011 ASA/AHA recommendations for the diagnosis of VCI	All

Dementia (NIA-AA)

is diagnosed when there is cognitive or behavioural symptoms which:

1. Interfere with function at work or usual activities
2. Represent a decline from previous function
3. Are not explained by delirium or major psychiatric disorder
4. Cognitive impairment is detected by:
   (a) history (person and knowledgeable informant)
   (b) mental status or bedside neuropsychological testing

5. The cognitive or behavioural impairment involves a minimum of 2 of the following domains

(a) memory

(b) reasoning, handling complex tasks, judgment

(c) impaired visuospatial function

(d) language

(e) changes in personality behaviour or comportment

McKhann G et al. Alzheimer's and Dementia 2011; 7: 263

Alzheimer's disease (probable) NIA-AA

- Dementia
- Insidious onset
- Clear cut history of worsening
- Initial and prominent cognitive deficits on history and examination in one of:

(a) amnestic presentation

(b) non amnestic presentation

language (PNFA)

visuospatial (PCA)

executive

Not probable AD if:

- Substantial evidence of cerebrovascular disease
- Core features of LBD
- Prominent features of Bv FTD
- Prominent features of semantic dementia or PPA
- Other neuro or non neuro illness or drugs

McKhann G et al Alz Dement 2011; 7: 263

MCI-clinical criteria NIA-AA

- Concern regarding a change in cognition (individual or observer)
- Impairment in one or more cognitive domains (typically 1-1.5 SD below)
- Preservation of independence in functional activities
- Not demented
- (Visual & language variants)

Albert M et al Alz Dement 2011; 7: 270

Vascular Cognitive Impairment: Probable VaD (NIA-AA)

- Dementia
- The deficits in ADL are independent of the motor/sensory sequelae of the vascular event.
- There is no history of gradually progressive cognitive deficits before or after the stroke that suggests the presence of a nonvascular neurodegenerative disorder.

Gorelick P et al. Stroke 2011; 42: 2672

Vascular Cognitive Impairment: Probable VaD

- There is cognitive impairment and imaging evidence of cerebrovascular disease and
- (a) There is a clear temporal relationship between a vascular event (e.g. clinical stroke) and onset of cognitive deficits, or
- (b) There is a clear relationship in the severity and pattern of cognitive impairment and the presence of diffuse, subcortical cerebrovascular disease pathology (e.g. as in CADASIL).

Gorelick P et al. Stroke 2011; 42: 2672

Definitions

Research recommendation:

For

We recommend the IWG definition of "asymptomatic at-risk for AD" states for research purpose.

All

We recommend reassessment of the utility of the concept of prodromal AD in the future when AD-PP biomarkers are available, validated, and ready for use in Canada.

All

A new lexicon of Alzheimer's Disease (IWG)

	AD diagnosis	Presence of impairment on specified memory tests	Evidence of biomarkers in vivo	Additional requirements
Typical AD	Yes	Required	Required	None
Atypical AD	Yes	Not required	Required	Specific clinical presentation
Prodromal AD	Yes	Required	Required	Absence of dementia
AD dementia	Yes	Required	Required	Presence of dementia
Mixed AD	Yes	Required	Required	Evidence of comorbid disorders
Preclinical AD				
Asymptomatic at risk for AD	No	Not present	Required	Absence of symptoms of AD
Presymptomatic AD	No	Not present	Not required	Absence of symptoms of AD and presence of monogenic AD mutation
Mild cognitive impairment	No	Not required	Not required	Absence of symptoms or biomarkers specific for AD

AD=Alzheimer's disease.

Table 2: Comparative features of the different conditions described in the new lexicon according to the new research criteria framework[5]

Dubois B et al. Lancet Neurol 2010; 9: 1118

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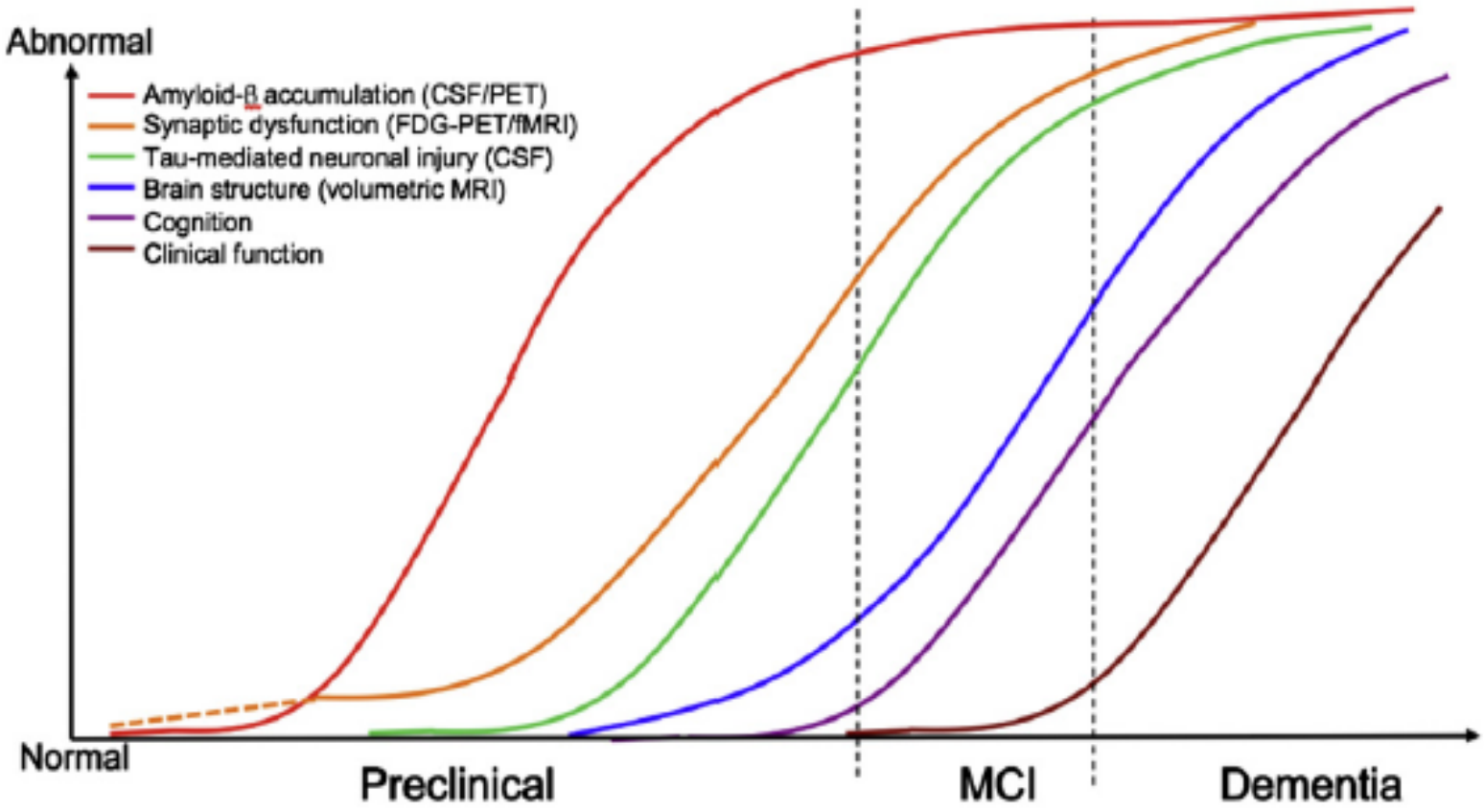
Dubois B et al. Lancet Neurol 2010; 9: 1118

Theoretical changes of biomarkers in AD

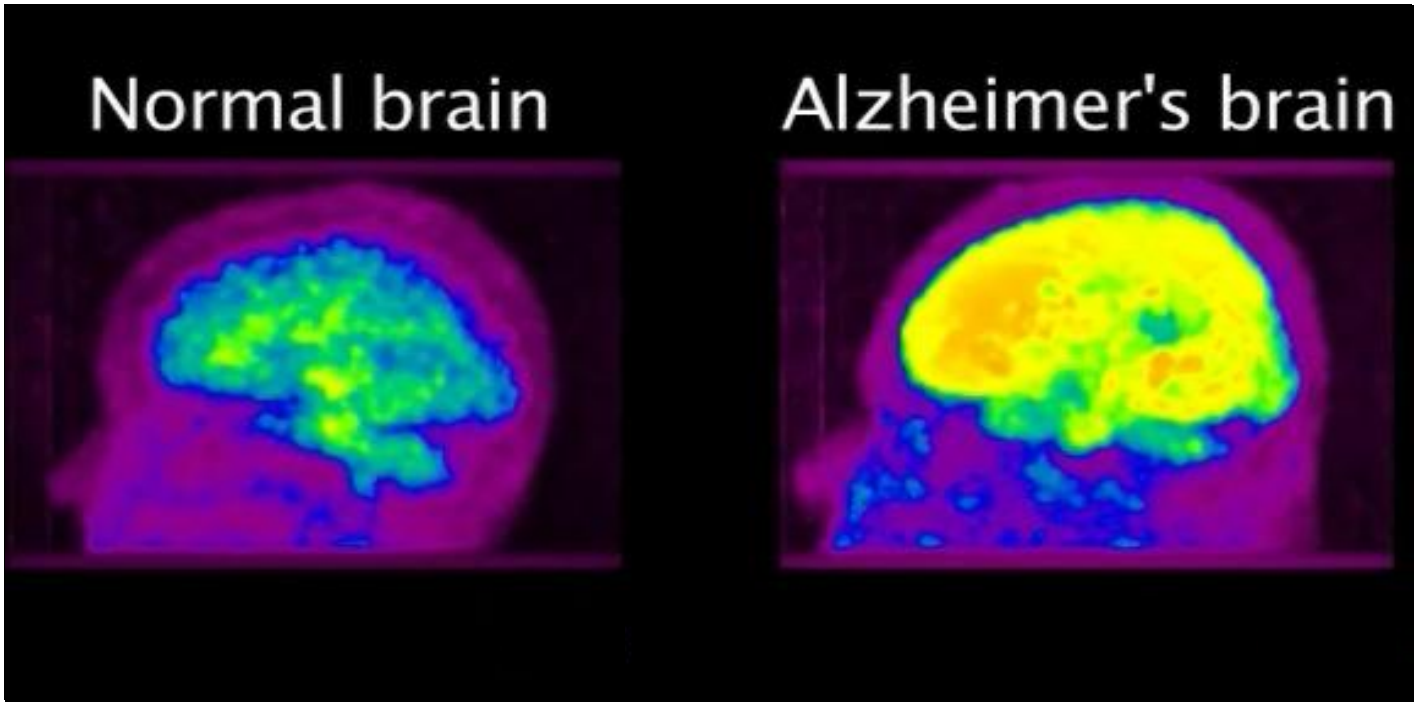


Sperling R et al Alz Dement 2011

Amyloid Imaging

with PiB (Pittsburg compound B)

Florbetapir now approved by FDA



Definitions

Given that the presence of brain amyloid in normal people is of uncertain significance, the CCCD discourages the use of amyloid imaging in individuals without memory loss, outside of the research setting .

For

The medical community should be clear in its discussions with patients, the media and the general population that presence of brain amyloid in normal people is of unclear significance at the present time.

All

Neuroimaging

J-P Soucy, R. Bartha, C. Bocti,
M. Borrie, A. Burhan, R. LaForce,
P. Rosa-Neto

Neuroimaging: Structural imaging: CT & MRI

	For	Against
For the assessment of a person with cognitive impairment, at least one structural imaging procedure (CT or MRI of the brain) is recommended to establish the presence of clinically unsuspected cerebrovascular disease and to rule out potentially reversible structural etiologies. (Grade 1B)	**26% (5)**	**74%(14)**
We suggest that a head MRI is preferred when a radiologist/neuroradiologist and/or a cognitive specialist (neurologist, geriatrician, or geriatric psychiatrist) can interpret patterns of atrophy and other features that may provide added diagnostic and predictive value as deemed appropriate by the specialist. (Grade 2B)	**90% (17)**	**10% (2)**

Neuroimaging: New indication for structural imaging: CT & MRI

For

All

In addition to previously listed indications for structural imaging , a CT or MRI should done in the assessment of a person with cognitive impairment *if the presence of unsuspected cerebrovascular disease* would change the clinical management.

Neuroimaging: Structural imaging: CT & MRI

	For	All
Standardization of clinical acquisition of core MRI dementia sequences is recommended in Canadian centres that have radiologists and cognitive specialists with expertise in assessing cognitive disorders, particularly when repeat MRI images can provide additional diagnostic, prognostic and safety information. (Grade 1B).		
We suggest that when available in the clinic, cognition specialists may use the computer images of the brain to educate a person with cognitive impairment and family members about changes in the brain. This knowledge may reinforce adherence to vascular risk factor management and to lifestyle modification to improve brain health. (Grade 2C).	**73.3% (11)**	**26.7% (4)**

Neuroimaging: FDG PET & SPECT

For a patient with a diagnosis of dementia *who has undergone the recommended baseline clinical and structural brain imaging evaluation and who has been evaluated by a dementia specialist but whose underlying pathological process is still unclear, preventing adequate clinical management,* we recommend that the specialist obtain a 18F-FDG PET scan for differential diagnosis purposes (Grade 1B).

For

All

For a patient with a diagnosis of dementia who has undergone the recommended baseline clinical and structural brain imaging evaluation and who has been evaluated by a dementia specialist but whose *underlying pathological process is still unclear, preventing adequate clinical management, and who cannot be practically referred for an 18F-FDG PET scan*, we recommend that a SPECT rCBF study be performed for differential diagnosis purposes (Grade 2C).

All

Neuroimaging: FDG PET & SPECT

For a patient with MCI evaluated by a dementia specialist and in whom clinical management would be influenced by evidence of an underlying neurodegenerative process, we suggest that an 18F-FDG PET scan be performed or, if not available, that a SPECT rCBF study be performed (Grade 2C).

For 72.2% (13)
Against 22.2% (4)
One abstention (5.5%)

For a patient with a diagnosis of dementia who has undergone the recommended baseline evaluation and who has been evaluated by a specialist but whose underlying pathological process is still undefined, and in whom 18F-FDG PET or SPECT rCBF imaging have not provided a satisfactory answer, we suggest that 131I-MIBG cardiac imaging be performed if differentiating between DLB or PD associated dementia and AD is needed for management purposes (evidence level: C)

For 22.2% (4)
Against 61% (11)
3 abstentions (16.7%)

Neuroimaging: FDG PET & SPECT

For

We recommend that *standardized acquisition/interpretation protocols* for both 18F-FDG PET and SPECT rCBF imaging in subjects with suspected neurodegenerative conditions be defined.

All

Neuroimaging: FDG PET & SPECT

	For	
Research recommendation:		
We suggest that 18F-FDG PET and SPECT rCBF imaging be used for enriching populations of controls and affected patients in therapeutic protocols evaluating the efficacy of dementia course-altering medications	**All**	
Research recommendation:		
We recommend that protocols for obtaining approval for clinical use of SPECT/PET markers of striato-nigral fibers integrity for application to the differential diagnosis of AD/DLB be launched	**87.5% (14)**	**12.5% (2)**

Neuroimaging: Amyloid Imaging

For

All

At present, there is *no clinical indication* for amyloid imaging in cognitively normal individuals, initial investigation of cognitive complaints, differentiating AD from other Aβ -associated dementia (e.g. DLB, CAA), differentiating between AD clinical variants (e.g. classic amnestic AD vs. PCA or lvPPA), and differentiating between non-AD causes of dementia (e.g. molecular subtypes of FTLD).

Neuroimaging: Amyloid Imaging

For

All

Amyloid imaging is not currently approved in Canada. Should amyloid imaging become available in Canadian clinicians in the future*, it must not be considered a routine test and we recommend it as an adjunct to a comprehensive evaluation for complex atypical presentations in referral to tertiary care Memory Clinics when a more accurate clinical diagnosis is needed* (Grade 1B).

Neuroimaging: Amyloid Imaging

	For
Should this technique become available to Canadian clinicians in the future, we recommend against its use in cognitively normal individuals or initial investigation of cognitive complaints (Grade 1B).	**All**
When faced with amyloid test results obtained outside Canada, physicians should be very cautious in their interpretation, i.e. used in isolation this test cannot diagnose AD, MCI, or differentiate normal from abnormal aging, and we recommend they consult with a dementia specialist familiar with this technique.	**All**

Neuroimaging: Amyloid Imaging

Although amyloid imaging represents a promising technique in the evaluation of dementia, there are many unknowns that could impact on its diagnostic utility and therefore we recommend that its use be restricted to research at present (Level 1C).

Health Policy recommendation:

Based on current evidence we recommend that Health Canada approves the use of amyloid imaging in tertiary care dementia clinics.

	For	Against
All	63% (12)	37% (7)

Neuroimaging: Amyloid imaging

For

Research recommendation:

All

Testing and longitudinal follow-up of asymptomatic individuals or patients with subjective cognitive impairments not meeting MCI criteria, or at-risk individuals (e.g. gene mutation carriers, family history of AD, ApoE ε4) should be restricted to research;

Research recommendation:

All

Future research should explore (1) the natural evolution of amyloid burden and its role in the pathophysiology of AD and other dementias, (2) its use as a potential surrogate marker for anti-amyloid therapies, (3) the value of new 18F amyloid tracers, (4) perform PETpathology correlations, and (5) compare amyloid imaging withCSF AD biomarkers as well as downstream markers of degeneration.

Neuroimaging: Amyloid Imaging

Research recommendation:

For

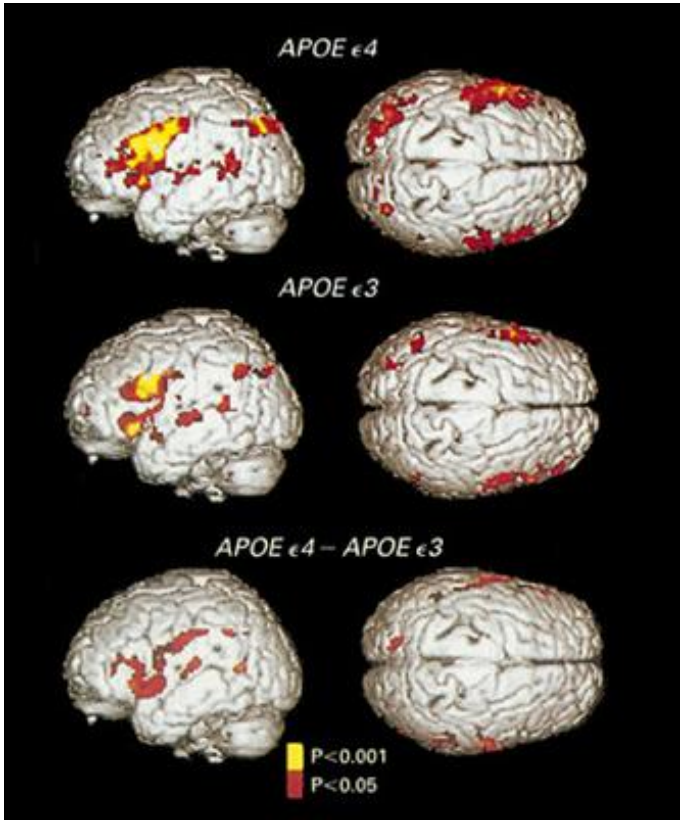
In research settings with amyloid imaging capabilities, investigators should be encouraged to develop projects that further validate the clinical and research uses of this technique and evaluate its readiness for translation to clinical care;

All

Research recommendation:

All

Trial designers are strongly encouraged to use this technique to (1) decrease the heterogeneity of their MCI population; (2) identify a cohort that is likely to respond to a drug with anti-amyloid properties; and (3) study patients that are likely
to convert to AD in a relatively short time frame;



Bookheimer S et al N Engl J Med 2000;343:450

Neuroimaging: Functional MRI

For

We recommend against the use of Functional MRI for the clinical investigation of patients presenting with cognitive complain (Grade1B)

All

Research recommendation:

Future studies should use standardized acquisition of images protocol and experimental paradigm to allow pooling of data. (Grade1C)

All

Research recommendation:

All

Future studies with large number of participants and longer period of follow-up are needed to allow firm conclusions on the value of fMRI in early detection of dementia and on predicting
conversion of MCI to AD (Grade1B)

Neuroimaging: Functional MRI

Research recommendation:
Future studies with large number of participants and longer period of follow-up are needed to allow firm conclusions regarding the value of fMRI in distinguishing between AD and non-AD dementia such as FTD and LBD (Recommendation level 1, evidence level B)

For All

Research recommendation:
Future studies with large number of participants and longer period of follow-up are needed to allow firm conclusions on the value of fMRI in assessing changes in brain activation in response to intervention such as cognitive training and pharmacotherapy (Recommendation level 1, evidence level C)

All

Neuroimaging: Functional MRI

For

All

Research recommendation:

Future studies with large number of participants and longer period of follow-up are needed to allow firm conclusions on the value of fMRI mapping brain activation in various neuropsychiatric and behavioural symptoms in the context of pre-clinical and clinical dementia such as depression, apathy and psychosis, which will help in developing specific treatments for these symptoms. (Grade 2C)

Neuroimaging: MR Spectroscopy

	For	All
Magnetic resonance spectroscopy shows promise for predicting which people with mild cognitive impairment are likely to progress to dementia. However, it is not currently recommended for clinical use to make or differentiate a diagnosis of dementia in people presenting with mild cognitive impairment (Grade 2C).		
1H MRS remains a promising technique for the identification of subjects with mild cognitive impairment who will convert to dementia. Further multi-site longitudinal studies should be conducted to establish normative values. Such studies should utilize standardized enrollment criteria, diagnosis criteria, data acquisition methods, and include automated analysis of spectra that incorporates proper prior knowledge of metabolite line shapes.	**93.8% (15)**	**6.3% (1)**

Neuroimaging: MR Spectroscopy

	For	
Standardized 1H MRS data acquisition and analysis methods should be developed in co-ordination with recommendations from the International Society of Magnetic Resonance in Medicine.	**93.8% (15)**	**6.3% (1)**
Future 1H MRS studies to demonstrate clinical effectiveness should utilize 3 Tesla MRI where available to increase data quality.	**93.8% (15)**	**6.3% (1)**

Neuroimaging: Other Markers

	For	Against
Imaging biomarkers of neuroinflammation or Tau pathology in dementia patients are not recommended in clinical practice.	**All**	
Although there is a growing body of literature supporting the use of dopamine presynaptic imaging agents for differentiating Lewy Body from AD disease, these imaging agents are not yet recommendable for clinical practice.	**84.6% (11)**	**15.4% (2)**

Liquid biomarkers

P.Rosa-Neto, G-Y R.Hsiung, M. Marsellis

Liquid Biomarkers

	For	Against
Plasma Aβ 1-42 levels are not recommended for clinical practice.	All	
Measures of CSF Aβ 1-42, total tau and phosphorylated tau at ser 181 are recommended for the biomarker workup of patients with atypical dementia.	64.3% (9)	35.7% (5)
Measures of CSF Aβ 1-42, total tau and phosphorylated tau at ser 181 should be collected following a specific protocol and the quantification must be carried out by an experienced lab with a validated technology and continuous participation in quality control programs.	71.4% (10)	28.6% (4)

Early Onset Dementia

S. Gauthier, D. Sadovnick, S. Black, G-Y R. Hsiung,
M. Masellis, S. Prasad, M. Williams, P. Rosa-Neto

Early Onset Dementia

	For
All patients with early onset dementia should be referred to a memory clinic, preferably one with access to genetic counselling and testing when appropriate.	**All**
The cost of genetic counselling and testing should be covered by public funding.	**All**
Physicians should be sensitive to the special issues associated with early onset dementia, particularly in regard to loss of employment and access to support services appropriate for that age group.	**All**

Early Onset Dementia

Research recommendations	For	Against
Considering the rarity of early onset dementia, a national registry for interested at risk individuals, mutation carriers and symptomatic patients will facilitate therapeutic research.	**88.9% (16)**	**11.1% (2)**
Health Policy recommendation:	**83.3% (15)**	**16.7% (3)**
This registry should be supported by public funding.		

Rapidly Progressive Dementia

C. Patterson, A. Rashed, G. Heckman, J. Crowson

Rapidly Progressive Dementia

	For	Against
It is suggested that RPD be defined as a dementia which develops within 12 months after the appearance of first cognitive symptoms. (Grade 2C)	**94.1% (16)**	**5.9% (1)**
It is suggested that individuals suspected of RPD be referred to physicians who are experienced and have access to the diagnostic facilities able to mount an organized and comprehensive diagnostic procedure. (Grade 2C)	**94.1% (16)**	**5.9% (1)**
After exclusion of delirium and evident underlying causes of RPD, it is suggested that a diagnostic strategy for RPD be based of the prevalence of causes of RPD in case series. (Grade 2B)	**All**	

Rapidly Progressive Dementia

	For	Against
The diagnostic strategy should emphasize the detection of potentially curable conditions, such as infections, immune mediated and toxic metabolic causes. Table 6 outlines such an approach. (Grade 2B)	**All**	
For individuals with AD, it is suggested that a decline of 3 or more points on the MMSE in 6 months, which identifies a group with a worse prognosis , is a signal to explore comorbid conditions and review pharmacological management. (Grade 2B)	**94.1% (16)**	**5.9% (1)**

Suggested approach to RPD

Procedure	Tests to be conducted on *all* RPD patients	Additional tests to consider
History	Onset, duration, associated features, comorbid conditions; exposures (tobacco, industrial chemicals, heavy metals, alcohol); complete medication review; past history and symptoms of systemic disease; travel history, sexual, recreational drug or blood products exposure; collateral history from close relatives; hallucinations, psychosis; fluctuating presentation; family history; headache; weight loss; skin rashes etc.	Collateral history from other sources; previous hospital admissions, other physicians; workplace; other relatives; search for evidence of cognitive "normality" at previous points in time.
Examination	Signs of systemic disease (any system, especially cardiovascular, pulmonary, GI, skin, rheumatological); optic fundi; neurological examination for focal signs; rigidity, motor disorders, cerebellar signs, myoclonus; physically examine all medications; cognitive testing	Full neuropsychological testing.
Laboratory	CBC, routine chemistry, Se. B12, Calcium, TSH, electrolytes, ESR, ANA, C-RP	HIV, VDRL, vasculitis screen, anti-thyroglobulin and anti-
	Urine analysis	thyroperoxidase antibodies, paraneoplastic antibodies (anti-Hu, anti-Ma, anti-Yo, anti Ri); drug levels, MMA. P-ANCA, C-ANCA;
Imaging	MRI with and without contrast; FLAIR and DWI Chest X-Ray	MR angiogram; CT chest, abdomen, pelvis PET scanning (e.g. FDG, florbetapir [only available in research settings])
CSF	Protein, glucose, IgG, VDRL, oligoclonal banding, cell count and differential	Cultures (bacterial including AFB; fungal) viral studies, protein 14-3-3, PS 100, cytology, Whipple PCR, Lyme serology; [amyloid β 1-42, total and phosphorylated tau may be available in some research settings]
EEG	Standard EEG	
Brain biopsy		Biopsy when diagnosis is essential and all above procedures have failed to establish diagnosis

Update on Pharmacological Treatment

N. Herrmann, K. Lanctôt, D. Hogan

Update on Pharmacological Treatment

	For
Many cases of dementia have more than one condition contributing to causation. Most commonly this will be a combination of Alzheimer's disease with other brain pathology. We recommend that management be based on what is (are) felt to be the predominant contributing cause(s). (Grade 1B)	**All**
We recommend cholinesterase inhibitors as a treatment option for Alzheimer's disease with cerebrovascular disease. (Grade 1B)	**All**

Update on Pharmacological Treatment

	For
Cholinesterase inhibitors are recommended as a treatment option for dementia associated with Parkinson's disease. (Grade 1A)	**All**
There is insufficient and inconsistent evidence on which to make a recommendation either for or against the use of the currently available cholinesterase inhibitors for the treatment of probable or possible vascular dementia. (Grade 2B)	**All**
All three cholinesterase inhibitors have demonstrated efficacy for *mild to severe* AD. We recommend a trial of a ChEI for most patients with AD. (Grade1A)	**All**

Update on Pharmacological Treatment

	For	Against
Direct comparisons do not suggest differences between cholinesterase inhibitors (Grade 2B). Selection of agent will be based on adverse effect profile, ease of use, familiarity, and differences between the agents in their pharmacokinetics and other mechanisms of action.	**94.1% (16)**	**5.9% (1)**
Combination therapy of a cholinesterase inhibitor and memantine is rational (as the medications have different mechanisms of action) and appears to be safe, but there is insufficient evidence to recommend for or against this combination (Grade 2B)	**All**	

DOMINO study: donepezil and memantine in mod/severe AD

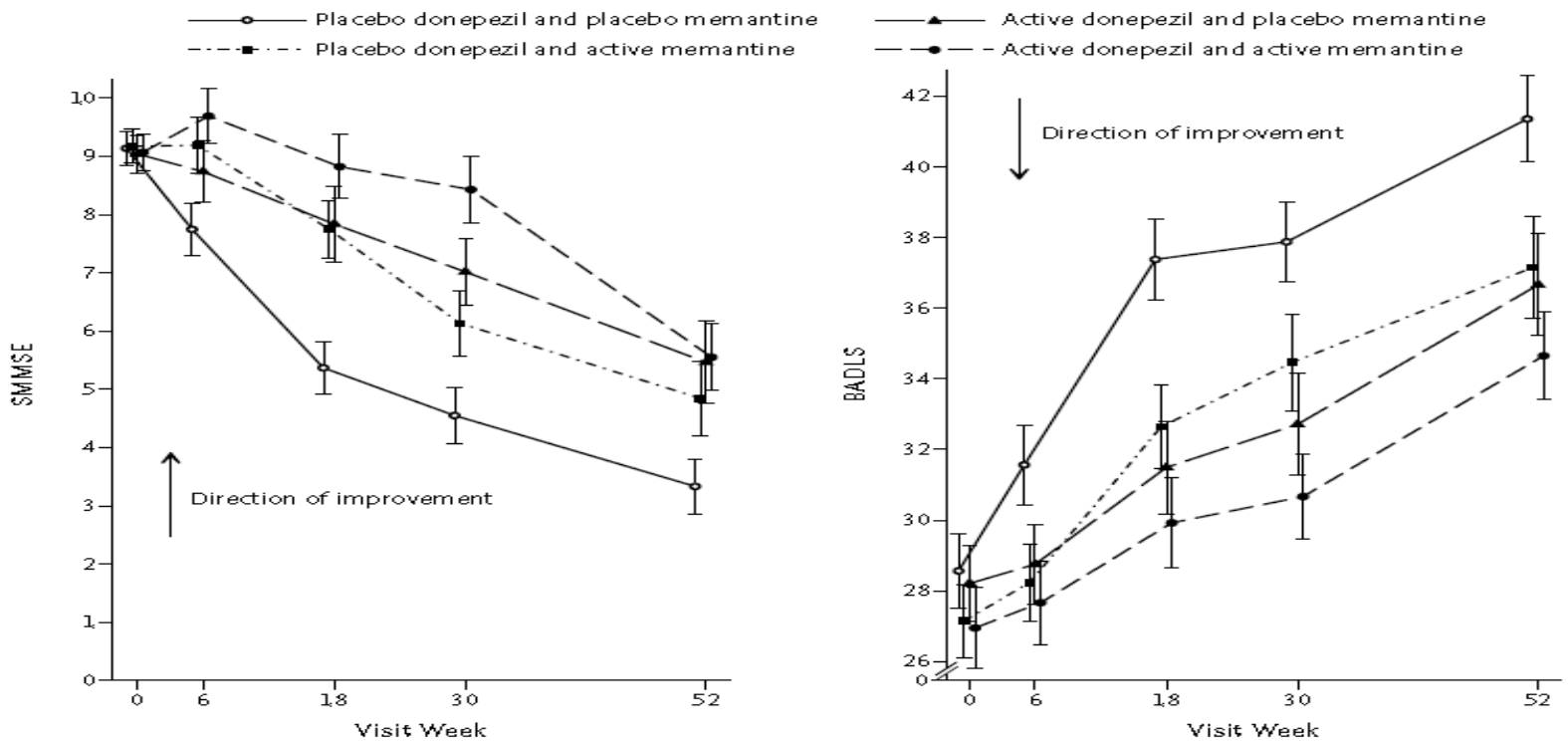


Figure 3. Mean Scores on the Standardized Mini–Mental State Examination (SMMSE) and the Bristol Activities of Daily Living Scale (BADLS), According to Visit Week and Treatment Group.

Scores on the SMMSE range from 0 to 30, with higher scores indicating better cognitive function; scores on the BADLS range from 0 to 60, with higher scores indicating greater impairment. Shown are raw estimates of the mean score at each visit. I bars denote the standard error.

Howard R et al. N. Engl J Med 2012; 366: 892

Update on Pharmacological Treatment

Discontinuing cholinesterase inhibitors in patients with moderate to severe Alzheimer's disease may lead to worse cognitive function and greater functional impairment as compared to continued therapy (Level 2B). This must be balanced with the risk for known side-effects and drug costs if therapy continues. It is suggested that cholinesterase inhibitors be discontinued when:

a) The patient and/or their proxy decision maker decide to stop after being appraised of the risks and benefits of continuation and discontinuation
b) The patient is sufficiently non-adherent with the medication that continued prescription of it would be useless, and it is not possible to establish a system for the administration of the medication to rectify the problem;
c) The patient's rate of cognitive, functional, and/or behavioural decline is greater on treatment compared to that prior to being treated;
d) The patient experiences intolerable side effects that are definitely or probably related to the cholinesterase inhibitor;
e) The comorbidities of the patient make continued use of the agent either unacceptably risky or futile (e.g., terminally ill); or,
f) The patient's dementia progresses to a stage (e.g., Global Deterioration Scale stage 7 [1]) where there would be no clinically meaningful benefit from continued therapy.

Continued – Next slide

Update on Pharmacological Treatment

	For	Against
When a decision has been made to discontinue therapy because of a perceived lack of effectiveness, it is suggested that the dose be tapered before stopping the agent and that the patient be monitored over the next 1-3 months for evidence of an observable decline. If this occurs, it is suggested that consideration be given to reinstating therapy. (Level 2C)	**83.3 (15)**	**6.7% (2)**
If the patient had an inadequate response to non pharmacological interventions or has a major affective disorder, severe dysthymia, or severe emotional lability, we recommend that a trial of an antidepressant could be considered. (Grade 2A)	**94.1 (16)**	**5.9% (1)**

Update on Pharmacological Treatment

	For
Based on good evidence we recommend that valproate should *not* be used for agitation and aggression in AD (Grade 1A)	**All**
There is no good evidence to recommend for or against the use of cholinesterase inhibitors and/or memantine for the treatment of *neuropsychiatric symptoms as a primary indication* (Grade 2B)	**All**

Update on Pharmacological Treatment

For

All

We suggest that risperidone, olanzapine and aripiprazole be used for severe agitation, aggression and psychosis associated with dementia where there is risk of harm to the patient and/or others. The potential benefit of all antipsychotics must be weighed against the significant risks such as cerebrovascular adverse events and mortality. (Grade 2A)

Update on Pharmacological Treatment

	For
There is insufficient evidence to recommend for or against the use of quetiapine in the management of severe agitation, aggression and psychosis associated with dementia (Grade 2B)	**All**
There is insufficient evidence to recommend for or against the use of SSRIs or trazodone in the management of agitated patients. (Grade 2B)	**All**

Dissemination and Knowledge Translation

Preplanned journal strategy

CDKTN

Health Plexus

Other

2012 CONFÉRENCE CANADIENNE CONSENSUELLE SUR LA DÉMENCE

2012 CANADIAN CONSENSUS CONFERENCE ON DEMENTIA

CLINICAL PRACTICE GUIDELINES/CONCENSUS STATEMENTS

Recommendations of the 4th Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (CCCDTD4)

Serge Gauthier, MD, Christopher Patterson, MD, Howard Chertkow, MD, Michael Gordon, MD, Nathan Herrmann, MD, Kenneth Rockwood, MD, Pedro Rosa-Neto, MD, PhD, Jean-Paul Soucy, MD on behalf of the CCCDTD4 participants*

McGill Center for Studies in Aging, Montreal, QC

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ABSTRACT

The 4th CCCDTD convened in May 2012 in Montreal with the primary aim of updating the previous diagnostic approach to AD, taking into account the revised diagnostic criteria proposed by the International Working Group (IWG) and the recommendations made by the National Institute on Aging—Alzheimer Association workgroups.

Key words: consensus, dementia, Alzheimer, diagnosis, imaging, symptomatic treatments

INTRODUCTION

Since 1989, three Canadian Consensus Conferences on the Diagnosis and Treatment of Dementia (CCCDTD)[1,2,3] have led to evidence-based recommendations on the diagnosis and treatment of Alzheimer's disease (AD) and related dementias. Previous CCCDTDs have attempted to make recommendations relevant to health professionals of all disciplines treating dementia (e.g., primary care practitioners, as well as neurologists, geriatricians, and psychiatrists). Recommendations have been published in medical journals reaching out to a wide readership (such as the *Canadian Medical Association Journal* (CMAJ), as well as more specialized readership (such as the *Canadian Journal of Neurological Sciences* and *Alzheimer's & Dementia*). Following the last CCCDTD in 2006, the CMAJ published a series of case-based articles with recommendations for each stage of AD (asymptomatic at risk,[4] mild cognitive impairment,[5] mild to moderate dementia,[6,7] and severe dementia[8]).

The 4th CCCDTD convened in May 2012 in Montreal with the primary aim of updating the previous diagnostic approach to AD,[9] taking into account the revised diagnostic criteria proposed by the International Working Group (IWG)[10,11] and the recommendations made by the National Institute on Aging—Alzheimer Association workgroups (NIA/AA)[12,13,14] to which a Canadian perspective has already been published.[15]

METHODS

The methodology of the meeting can be summarized as follows: The process was guided by the tenets of the AGREE collaboration to which 20 of the 23 criteria were met.[16] While previous CCCDTDs had used the evidence grading system developed by the Canadian Task Force on Preventive Health Care, for this iteration we attempted to follow, where possible, the GRADE system, in keeping with current recommendations for the conduct of consensus conferences.[17]

Complete background articles written by workgroups were posted to a password-protected website, accessible to all conference participants, who were encouraged to post comments. The recommendations, modified where appropriate as a result of participants' comments, were then posted for online voting. Organizations relevant to the care of people with dementia were approached to appoint delegates. These delegates had full access to the background articles, were encouraged to comment, and were allowed to vote on recommendations. Online voting was closed one day before the conference assembly, which was held in Montréal on May 4th and 5th, 2012. At the conference, each topic was briefly reviewed before voting was carried out on each recommendation. All participants (except for the four industry observers) were permitted to vote. In the event of failed consensus, online votes of conference participants who were not able to attend the assembly were taken into account. As in each previous consensus conference, consensus was defined as 80% or more of conference participants voting

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4th Canadian Consensus Conference on the Diagnosis and Treatment of Dementia

S. Gauthier, C. Patterson, H. Chertkow, M. Gordon, N. Herrmann, K. Rockwood, P. Rosa-Neto, J.P. Soucy on behalf of the CCCDTD4 participants.*

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Most of the recommendations are particularly relevant to specialists treating patients with dementia because of the nature of the topics discussed: definitions/new diagnostic criteria for AD, use of neuroimaging and of liquid biomarkers, early onset dementia, rapidly progressive dementia. These recommendations will be published on line in the Canadian Journal of Geriatrics in November 2012. Symptomatic treatments, which are relevant to all treating physicians, and are also reported in this article.

Definitions/new diagnostic criteria

The motivation to revise criteria in Canada was the evolution of thinking about how dementia might be approached in light of new criteria in the United States. A proposal was made by the IWG led by Bruno Dubois and Howard Feldman to diagnose AD even before dementia has become manifest, using a specific clinical phenotype (memory impairment of the hippocampal type) and a biomarker[10]. In 2011 three workgroups of the NIA/AA recommended criteria for the diagnosis of dementia caused by AD[12], MCI due to AD[13], and asymptomatic AD[14]. The latter has most clearly embraced the Dubois/Feldman proposal

CCCDTD4 participants: * A. Al Kashef, B. Bartha, H. Bergman, J. Bethell, S. Black, C. Boal, M. Borrie, A. Burham, C. Cook, J. Crowson, M. Donnelly, H. Feldman, G. Hackman, D. Hogan, G.Y.R. Hsiung, G. Inglis, C. Jacova, R. Lafrance, K. Lanctôt, L. Lee, K. Leslie, M. Masellis, F. Massoud, A. Moore, S. Pasand, K. Rabheru, D. Sahlomick, L. Trudeau, J. Vedel, M. Williams.

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Correspondence to: Serge Gauthier, McGill Center for Studies in Aging, 6825 LaSalle Blvd, Montreal, Quebec, H4H 1R3, Canada. Email: Serge.gauthier@mcgill.ca.

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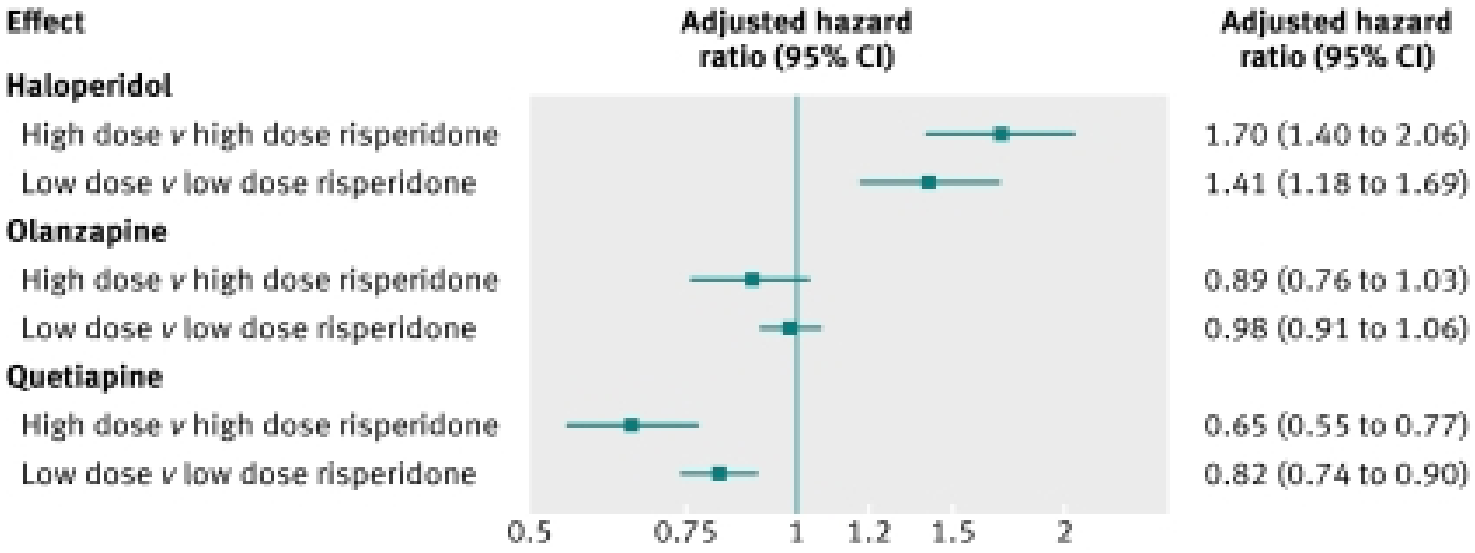
What's New from the Canadian Consensus Conference on the Diagnosis and Treatment of Dementia (CCCDTD4)

Summary

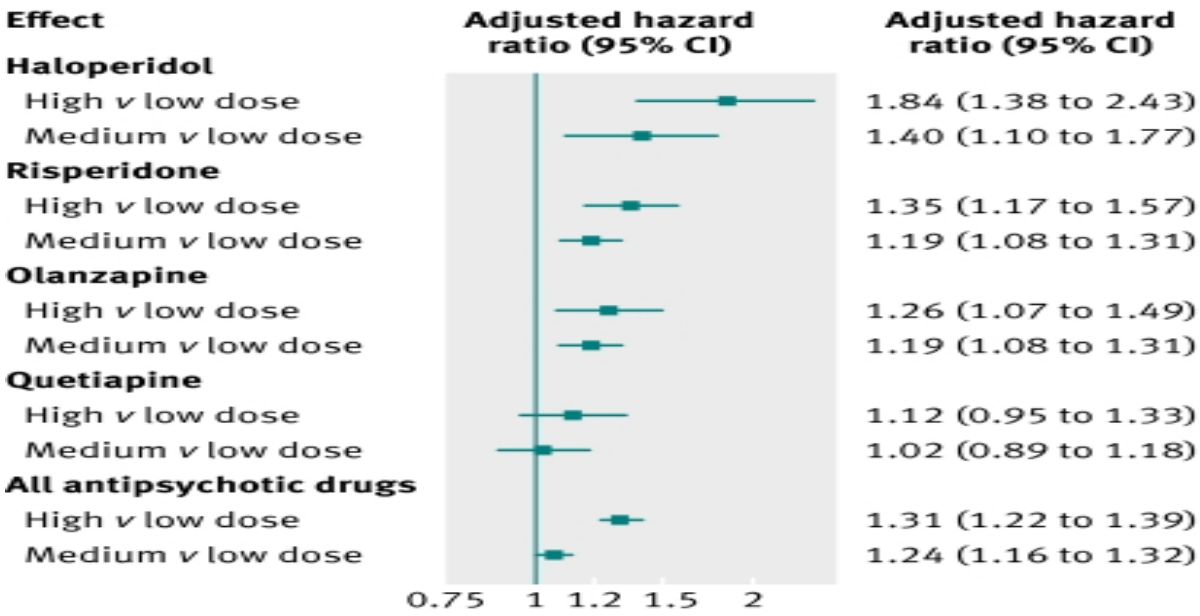
- Emergence of CSF and neuroimaging biomarkers have prompted new recommendations for clinical practice
- Clinical definitions are little changed
- Few new pharmacological recommendations (valproate, memantine)
- EOD and RPD recommendations
- Extensive research agenda

Differential risk of death associated with antipsychotics



Huybrechtsk K et al BMJ Feb 23. 344.e977

Differential risk of death associated with antipsychotics



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Mortality risk with antipsychotics

30,000 DVA over age 65 with dementia

Exposure Analysis	Adjusted, Unweighted		
Risperidone	1.00		
Haloperidol	1.59	1.36–1.85	<0.0001
Olanzapine	1.06	0.93–1.22	0.3954
Quetiapine	0.74	0.65–0.83	<0.0001

Kales H et al. Am J Psychiatr 2012; 169: 71

MCI criteria incorporating biomarkers

Diagnostic category	Biomarker probability of AD etiology	Aβ (PET or CSF)	Neuronal injury (tau, FDG, sMRI)
MCI–core clinical criteria	Uninformative	Conflicting/indeterminant/untested	Conflicting/indeterminant/untested
MCI due to AD—intermediate likelihood	Intermediate	Positive	Untested
		Untested	Positive
MCI due to AD—high likelihood	Highest	Positive	Positive
MCI—unlikely due to AD	Lowest	Negative	Negative

Abbreviations: AD, Alzheimer's disease; Aβ, amyloid beta peptide; PET, positron emission tomography; CSF, cerebrospinal fluid; FDG, fluorodeoxyglucose; sMRI, structural magnetic resonance imaging.